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Convergent Synthesis of a Complex Oxime Library Using Chemical Domain Shuffling

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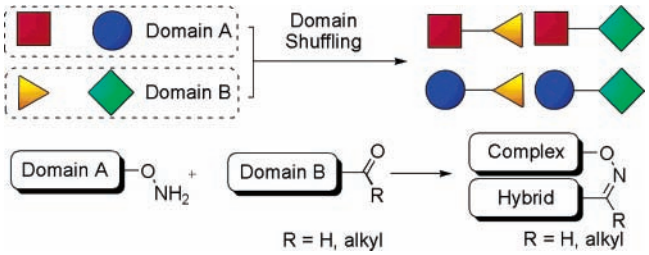
ABSTRACT



The synthesis of a complex hybrid oxime library is reported utilizing convergent ligation of alkoxyamine and carbonyl monomers via "chemical domain shuffling". Initial biological screening of the library against human small cell lung carcinoma (A549) cells led to the identification of a novel hybrid dimer in contrast to the corresponding monomeric compounds which were found to be inactive.

The synthesis of chemical libraries rich in structural diversity is an emerging field with immediate applications in biomedical research.[1] Strategies for library synthesis have mainly focused on combinatorial synthesis of molecules that vary substituents on a core structural type.[2] Diversity-oriented synthesis is a new strategy for constructing libraries with both skeletal and functional group diversity.[3] In an effort to formulate novel approaches to complex library synthesis, we have taken a number of lessons from biologically active, hybrid molecules[4] (Figure 1). For example, thiomarinol (**1**),[5] a natural product hybrid of pseudomonic acid and the pyrrothine antibiotic holothin, displays more potent antimi-

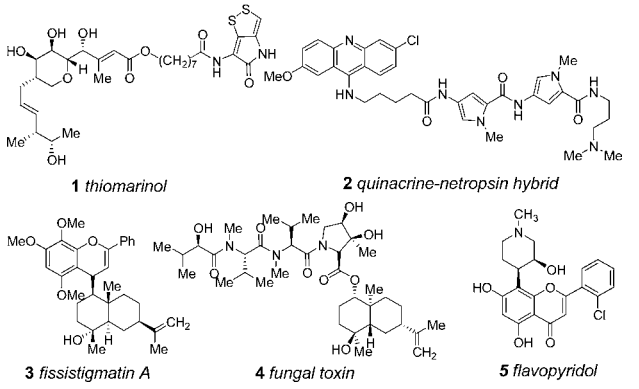


Figure 1. Hybrid molecules with variable chemical domains.

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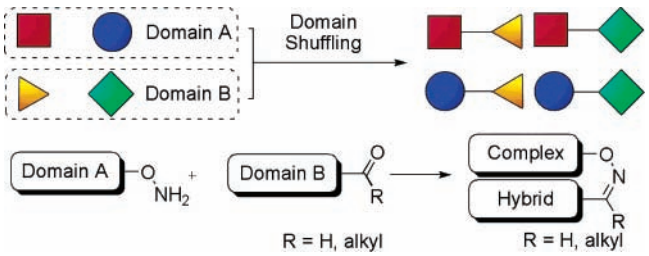
crobial activity than either of the parent fragments. The potential for hybrid molecules to possess enhanced biological activity is also supported by the recent preparation of synthetic hybrid molecules.[6] For example, a quinacrine−netropsin hybrid molecule **2** was found to enhance C1027-induced DNA cleavage by combining the DNA sequence selectivity of netropsin and the cell permeability and DNA binding affinity of quinacrine to sensitize DNA toward C1027 cleavage.[7] Further examination of hybrid molecular structures illustrates the interchange of discrete chemical domains. For example, the natural product fissistigmatin A (**3**)[8] is a eudesmane−flavone hybrid, whereas the fungal toxin (**4**)[9] is a eudesmane−peptide hybrid natural product. In addition, the CDK inhibitor flavopyridol (**5**)[10] has identifiable flavone and piperidyl domains. Inspired by these and related hybrid molecules, we have considered a convergent[11] approach to library synthesis involving "*chemical domain shuffling*". In this approach, discrete fragments or "chemical domains" may be "shuffled"[12] to prepare complex hybrid structures (Scheme 1). Herein, we report the successful implementation of this approach in the construction of a library of hybrid oximes[13,14] from complex alkoxyamine and carbonyl domains.

To demonstrate convergent synthesis of a complex hybrid oxime library using chemical domain shuffling, we prepared 26 monomer fragments emphasizing both structural and stereochemical complexity. Approximately 10 chemotypes were represented per monomer set (Figure 2).[15] Alkoxyamine

Scheme 1. Convergent Library Synthesis Using Chemical Domain Shuffling



monomers included β-hydroxy alkoxyamines (**6**), pyrans (**7**−**10**), carbohydrate-derived alkoxyamines (**11** and **12**), and heterocyclic alkoxyamines[13] (**13**−**17**). Carbonyl-containing monomers included naphthyridines and pyridoazepines[16] (**18**−**21**), complex pyrans (**22**−**24**), polyketide-like fragments (**25**−**27**), angular scaffolds (**28** and **29**), benzopyrans (**30**), and pipecolate esters[17] (**31**).

Representative monomer syntheses are illustrated in Scheme 2 (**a**−**d**). Starting from the readily available furan-containing epoxide **32**,[18] phthalimide-protected alkoxyamine **33** was prepared in high yield and excellent optical purity (95% ee) under the mediation of a Co−oligosalen catalyst.[19] Subsequent phthalimide deprotection using PS-ethylenediamine[20] afforded alkoxyamine **13** without further purification. For the synthesis of naphthyridine-containing ketone **18**, $CpCo(CO)_2$-catalyzed[21] intermolecular [2 + 2 + 2] cyclocondensation of alkynyl nitrile **34**[22] and diphenylacetylene **35** was conducted to afford naphthyridine **36**. $Yb(OTf)_3$-mediated[23] Michael addition of **36** to methyl vinyl ketone provided the desired β-amino ketone **18**. To prepare polyketide-like alkoxyamine **6** and aldehyde **27**, a three-component asymmetric crotylation[24] of aldehyde **37**, silyl ether **38**, and chiral silane **39** was employed to prepare

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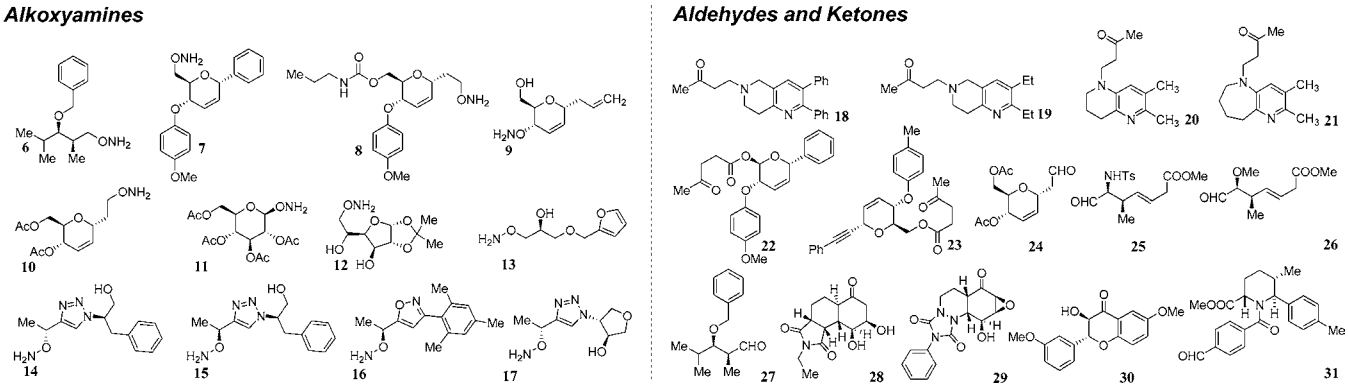
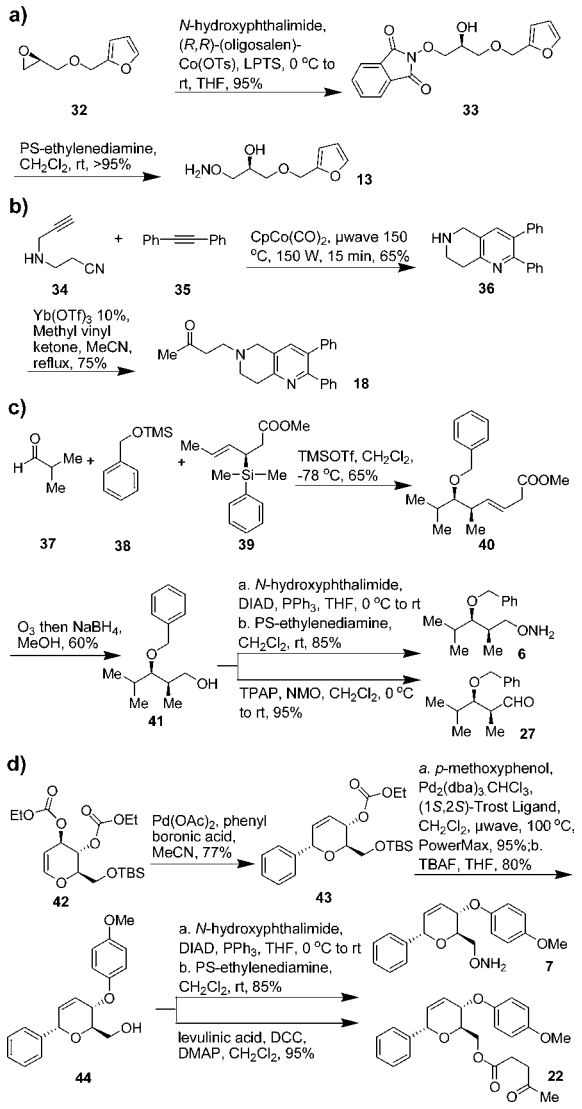


Figure 2. Alkoxyamine and carbonyl fragments utilized in chemical domain shuffling.

homoallylic ether **40**. Ozonolysis of **40**, followed by reduction using $NaBH_4$, afforded alcohol **41**. This central intermediate was subjected to *N*-alkoxyphthalimide formation using Mitsunobu conditions, followed by phthalimide deprotection,[20] to afford alkoxyamine **6**. Alternatively, TPAP-mediated[25] oxidation of **41** afforded aldehyde **27**, illustrating the use of a common building block for alternate preparation of carbonyl and alkoxyamine domain monomers. For preparation of alkoxyamine **7** and ketone **22**, allylic carbonate **43** was generated employing palladium-catalyzed addition of phenyl boronic acid to glycal **42**.[26] Diastereoselective phenol addition ($Pd_2(dba)_3$·$CHCl_3$, (1*S*,2*S*)-(−)-1,2-diaminocyclohexane-*N*,*N*′-bis-(2′-diphenylphosphinobenzoyl)),[27] followed by desilylation, provided alcohol **44**. The stereochemical assignment of **44** was based on X-ray crystallographic analysis of a related derivative.[15] Primary alcohol **44** was transformed to the corresponding alkoxyamine **7** and keto ester **22**, the latter via acylation with levulinic acid.

Scheme 2. Representative Monomer Syntheses



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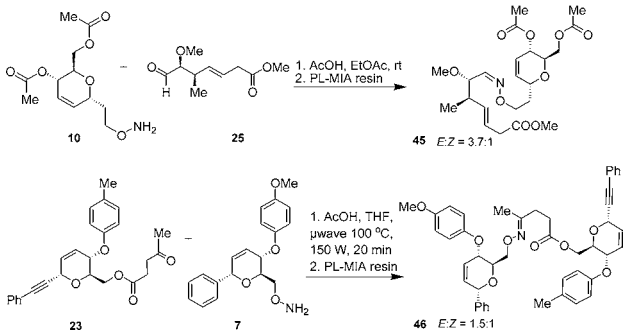
Scheme 3. Representative Complex Oxime Syntheses



reactions with alkoxyamine **12** to avoid decomposition. An analytical scale rehearsal employing one alkoxyamine and five ketones (3.0 μmol of ketone) was performed to further evaluate optimized conditions for complex oxime formation.[15] Polymer-supported methylisatoic anhydride (PL-MIA)[29] was utilized to scavenge excess alkoxyamines. Following the optimized oxime formation conditions, greater than 95% purity was obtained for all 5 hybrid oximes synthesized in the analytical rehearsal after resin scavenging.

Preparative-scale (0.019 mmol) library synthesis was next conducted using chemical domain shuffling of a 14 × 12 array of monomers to produce a library of 168 complex hybrid oximes. Representative conditions for oxime formation reactions are shown in Scheme 3. After scavenging with PL-MIA resin, 161 products (96%) were found to have purities greater than 95% as indicated by HPLC-ELSD analysis (isolated yields 49%−99%, 160 reactions >85%). Representative library members are shown in Figure 3 and illustrate ligation between pyran−polyketide (**45**), bis-pyran (**46** and **48**), 1,5-naphthyridine−triazole (**53**), and benzopyran−triazole (**56**) domains. ^{1}H NMR analysis of randomly selected library members (Figure 3) indicates that a significant number of hybrid oximes exist as inseparable mixtures of *E*/*Z* isomers.[15] The corresponding acetone oximes of alkoxyamine monomers and the *O*-methylhydroxylamine oximes of the ketone/aldehyde monomers were also prepared for comparison to hybrid dimers in subsequent biological screening.

The 168-member library and 26 monomer derivatives were assayed for human small cell lung carcinoma (A549) growth inhibition. Previous studies have reported the rapid isomerization of aldehyde-derived oximes in polar media, which should permit selection of the most active oxime isomer by biological targets of interest.[14g] Compound **47** (Figure 3) was found to inhibit growth of A549 cells with an IC_{50} value of 6.2 μM. Interestingly, the corresponding monomeric acetone oxime of **16** and *O*-methylhydroxylamine oxime of **29** exhibited no antiproliferative activity. This preliminary result indicates that ligation of two discrete chemical domains may be used to generate complex structures with novel biological activities.[4,6]

In summary, we have successfully synthesized a complex oxime library via "chemical domain shuffling", an under-

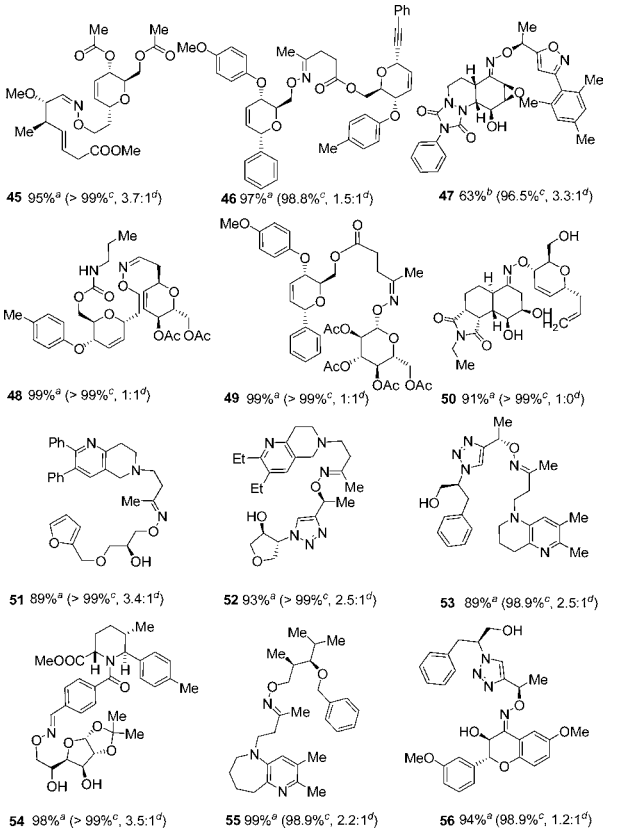


Figure 3. Representative library members.

developed approach for library synthesis involving interchange of chemical motifs through convergent ligation. Further biological evaluation of the complex oxime library and additional applications of chemical domain shuffling to generate complex chemical libraries which address novel chemical space[30] are currently in progress

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Supporting Information Available: Experimental procedures and characterization data for all new compounds including X-ray crystal structure coordinates. X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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